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Improved Survival of Patients With Melanoma Brain Metastases in the Era of Targeted BRAF and Immune Checkpoint Therapies

Sarah Sloat, MD^{1,2}; Yian A. Chen, PhD³; Xiuhua Zhao, PhD³; Jamie L. Weber, MD⁴; Jacob J. Benedict, MD⁴; James J. Mulé, PhD⁵; Keiran S. Smalley, PhD^{2,6}; Jeffrey S. Weber, MD, PhD⁷; Jonathan S. Zager, MD^{2,8,9}; Peter A. Forsyth, MD^{10,11}; Vernon K. Sondak, MD^{2,8,9}; and Geoffrey T. Gibney, MD¹²

BACKGROUND: The development of brain metastases is common for systemic treatment failure in patients with melanoma and has been associated with a poor prognosis. Recent advances with BRAF and immune checkpoint therapies have led to improved patient survival. Herein, the authors evaluated the risk of de novo brain metastases and survival among patients with melanoma brain metastases (MBM) since the introduction of more effective therapies. **METHODS:** Patients with unresectable AJCC stage III/IV melanoma who received first-line systemic therapy at Moffitt Cancer Center between 2000 and 2012 were identified. Data were collected regarding patient characteristics, stage of disease, systemic therapies, MBM status/management, and overall survival (OS). The risk of de novo MBM was calculated using a generalized estimating equation model and survival comparisons were performed using Kaplan-Meier and Cox proportional analyses. **RESULTS:** A total of 610 patients were included, 243 of whom were diagnosed with MBM (40%). Patients with MBM were younger, with a lower frequency of regional metastasis. No significant differences were noted with regard to sex, *BRAF* status, or therapeutic class. The risk of de novo MBM was found to be similar among patients treated with chemotherapy, biochemotherapy, BRAF-targeted therapy, ipilimumab, and anti-programmed cell death protein 1/programmed death-ligand 1 regimens. The median OS of patients with MBM was significantly shorter when determined from the time of first regional/distant metastasis but not when determined from the time of first systemic therapy. The median OS from the time of MBM diagnosis was 7.5 months, 8.5 months, and 22.7 months, respectively, for patients diagnosed from 2000 to 2008, 2009 to 2010, and 2011 to the time of last follow-up ($P = .002$). **CONCLUSIONS:** Brain metastases remain a common source of systemic treatment failure. The OS for patients with MBM has improved significantly. Further research into MBM prevention is needed. *Cancer* 2018;124:297-305. © 2017 American Cancer Society.

KEYWORDS: BRAF, brain metastasis, immunotherapy, melanoma, targeted therapy.

INTRODUCTION

Greater than one-third of patients with advanced melanoma will develop brain metastases during the course of their disease, and even higher rates have been observed at the time of autopsy.¹⁻³ Historically, the prognosis of patients with melanoma brain metastases (MBM) has been poor, with a median overall survival (OS) ranging from 3 months to 6 months from the time of diagnosis.^{1,2,4,5} Patients with solitary or oligometastatic disease amenable to surgery or stereotactic radiosurgery (SRS) are reported to have better survival, with a reported median OS ranging from 7 months to 10 months.⁶ To the best of our knowledge, there currently is no method with which to accurately predict who will develop MBM. However, various parameters are associated with an increased risk (eg, melanoma arising from head and neck areas; ulcerated primary tumors; elevated serum lactate dehydrogenase levels; and, possibly, molecular alterations in *BRAF*, *NRAS*, or *PTEN*).^{2,5,7,8}

The brain has been a prominent site of treatment failure with systemic therapies for patients with advanced melanoma. In a prospective study evaluating the incidence of MBM between patients treated with the combinations of

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cisplatin, temozolomide, and interleukin 2 (IL-2) and cisplatin, dacarbazine, and IL-2, approximately 49% of assessable patients with melanoma developed central nervous system (CNS) disease with no significant difference noted between treatments.⁹ Similarly, MBM progression has been reported as a primary recurrence site in up to one-half of patients who initially responded to IL-2.¹⁰ These observations may be due to historically low rates of controlling systemic disease (ie, prevention of tumor seeding to the brain), as well as the poor CNS penetration and MBM activity of many systemic therapies.¹¹ Among chemotherapies with modest CNS activity (eg, temozolomide and fotemustine), studies have shown objective MBM response rates ranging from 7% to 12%.¹² Similar disappointing results were observed among patients treated with high-dose IL-2.^{13,14}

New immune checkpoint and BRAF/MEK-targeted therapies have demonstrated greater clinical activity in patients with metastatic melanoma. The median OS has now reached 2 years and longer in studies of BRAF/MEK combination therapy and anti-programmed death-ligand 1 (PD-1) regimens.¹⁵⁻¹⁷ Phase 2 trials of these agents in patients with active MBM also have demonstrated promising intracranial activity, with objective MBM response rates as high as 22% with pembrolizumab and 31% with dabrafenib (*BRAF V600E*-mutant population).¹⁸⁻²¹ Although these findings suggest that improved outcomes among patients with melanoma could be due in part to a reduction in CNS failure with enhanced extracranial disease control and/or CNS activity, the brain has been reported to still be a common site of treatment failure for BRAF-targeted therapy.^{22,23} Therefore, to our knowledge, it remains unclear whether MBM incidence rates significantly differ among newer targeted and immune therapies compared with prior treatment strategies and if patient survival continues to be significantly impacted by the development of MBM.

The primary objective of the current study was to investigate the association between systemic therapy regimens and de novo MBM development in patients with advanced melanoma treated with chemotherapy, biochemotherapy, IL-2, BRAF-targeted agents, or immune checkpoint blockade. The secondary objectives were to compare the OS in patients with advanced melanoma with and without brain metastases and assess prognostic factors in patients with MBM who were treated with new targeted and immune therapy strategies.

MATERIALS AND METHODS

The current study was a retrospective cohort study of patients with unresectable metastatic melanoma

(cutaneous/unknown primary tumor, uveal, or of mucosal origin) who were treated with systemic therapy at the Moffitt Cancer Center in Tampa, Florida. To include a comprehensive sample size, patients were identified using a combination of pharmacy treatment records, *BRAF* genotyping records, and clinical trial enrollment. Inclusion requirements were AJCC stage III or stage IV melanoma, the initiation of systemic therapy between 2000 and 2012 to allow for long-term follow-up, and at least 2 months of follow-up while receiving first-line systemic therapy. Data were collected regarding patient demographics, clinical/pathologic data concerning the primary melanoma and subsequent metastases, systemic therapy, and OS. Patients with unknown primary tumors were added to the cutaneous group based on recent literature unless there was a suspicion by the treating investigator that the tumor was not cutaneous in origin.^{24,25} Patients then were divided in 3 groups (2000-2008, 2009-2010, and from 2011 onward) based on the introduction of targeted therapies. Between 2009 and 2010, an increasing number of checkpoint/targeted therapy trials became available and 2011 was the year ipilimumab and vemurafenib were approved. This also divided the patients into approximately equal groups for statistical analyses.

Because of the range of systemic therapies that the patients received, both standard therapies and clinical trial agents, 7 categories were used to represent generalized treatment approaches available in clinical practice. These included chemotherapy regimens (monotherapy and combinations), biochemotherapy regimens (eg, concurrent cisplatin, vinblastine, dacarbazine, IL-2, and interferon- α -2b used in Eastern Cooperative Oncology Group study E3695 or similar),²⁶ IL-2, ipilimumab (allowed for combined ipilimumab plus other non-checkpoint immunomodulators such as interferon), anti-PD-1/programmed death-ligand 1 (PD-L1) therapies (eg, pembrolizumab and nivolumab as monotherapy or in combination with other nonimmune checkpoint stimuli such as a multi-peptide vaccine), and BRAF-targeted therapy (selective BRAF inhibitor monotherapy, MEK inhibitor monotherapy, and combination BRAF plus MEK inhibitors). The remaining group ("Other") contained all regimens that did not fit exclusively into one of these categories (eg, dendritic cell vaccines, combination regimens on protocol such as carboplatin, paclitaxel, and sorafenib and ipilimumab and vemurafenib). This group also contained a patient receiving treatment with ipilimumab and nivolumab. The study was approved by the Institutional Review Board of the University of South Florida. Patients with MBM were defined as patients who developed

MBM at any time during follow-up, regardless of preceding and subsequent treatments. Patients developing MBM before the initiation of systemic treatment were classified as being diagnosed before the initiation date of first systemic therapy. Patients with MBM who never received systemic treatment during the course of their disease were not captured.

Statistical Analysis

Descriptive statistics were summarized for age, sex, primary melanoma type, *BRAF* status, and systemic therapy received for all patients and classified by MBM status. The first set of analyses focused on assessing the association between variables of interest related to the development of MBM. Clinical and demographic characteristics between populations with and without MBM were compared. Proportion differences between the 2 populations were investigated using chi-square tests for categorical variables. Monte Carlo-estimated *P* values for the exact test were reported when $\geq 50\%$ of the cells had expected counts < 5 . The median differences between the MBM and MBM-free populations for continuous variables (eg, age) were compared using Wilcoxon rank-sum tests. We then evaluated the association between treatment (coded as the 7 categories of therapy as described above), systemic treatment line (first-line, second-line, and third-line therapies only), age at the time of first systemic treatment, and the development of MBM using a generalized estimating equation (GEE) model. Because patients often received > 1 line of systemic therapy, the GEE model was performed to evaluate the correlation between each line of therapy and MBM event in the same patient. Patients with recurring MBM were censored for subsequent therapies. For example, a patient who was free of MBM while receiving ipilimumab as first-line therapy but then developed MBM during second-line therapy with a *BRAF* inhibitor would have been classified as a negative event followed by a positive event. The third-line therapy in this patient would not have been included in the model.

OS, defined as the duration between the time of first diagnosis of regional or distant metastatic disease to the date of death, was evaluated in both patients with and without MBM using the Kaplan-Meier method. Survival differences between the 2 populations were determined using a log-rank test. This survival analysis was repeated using time zero as the date of first systemic therapy. Subsequent survival analyses were focused on the survival of patients with MBM, which was calculated from the date of diagnosis of MBM to the date of death. The Kaplan-Meier method as well as univariate and multivariate Cox

proportional hazards regression models were used to determine whether variables were associated with OS and to obtain hazard ratios (HRs) and their 95% confidence intervals (95% CIs). All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC). A 2-sided *P* value $\leq .05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 1016 patients initially were evaluated for inclusion into this data set. Patients were excluded because of there being < 2 months of follow-up after the initiation of systemic treatment (245 patients), no digital records available (116 patients), a nonmelanoma cancer diagnosis (40 patients), multiple melanoma primary tumors (which confounded start dates; 4 patients) and a missing date of diagnosis (1 patient). A total of 610 patients were included in the database (see Supporting Information Fig. 1). The median follow-up was 27.6 months from the time of first regional or distant metastasis.

Of the 610 patients included in the data set, 243 patients (39.8%) developed MBM. The median time from the initial melanoma diagnosis to the first diagnosis of MBM was 29.6 months (range, 0-320.2 months). Patients with MBM were significantly younger than patients without MBM at the date of first metastasis (median age, 58 years vs 62 years; $P \leq .0001$) (Table 1). There was a significant difference in the primary melanoma subtypes between patients with MBM and those without MBM ($P = .02$) (Table 1), which was largely driven by the low number of patients with MBM with a mucosal primary site ($P = .008$). In addition, patients in the MBM population were less likely to have regional metastasis (stage III) as the first site of metastasis ($P < .0001$). Otherwise, there were no significant differences noted with regard to sex, *BRAF* status, or class of systemic treatments received between the patients with and without MBM.

The first MBM event was most often diagnosed early in the disease (ie, before systemic therapy [31.7%] or during first-line treatment [35.4%]), as shown in Supporting Information Table 1. Neurologic symptoms were present in 53.5% of patients at the time of MBM diagnosis. Karnofsky performance status (KPS) was $> 70\%$ in 59.7% of patients. The majority of patients (48.1%) had 1 MBM at the time of diagnosis, 34.6% had 2 to 4 MBM at the time of diagnosis and 16.5% of patients had ≥ 5 MBM and/or leptomeningeal disease. The most frequent treatment for

TABLE 1. Patient Characteristics

Characteristic	Overall N=610	MBM Population N=243	MBM-Free Population N=367	P
Median age (range), y ^a	60 (15-92)	58 (15-86)	62 (19-92)	<.0001
Male sex, no. (%)	400 (65.6%)	159 (65.4%)	241 (65.7%)	1.0
Primary melanoma type, no. (%)				.02
Cutaneous	583 (95.6%)	239 (98.4%)	344 (93.7%)	
Mucosal	19 (3.1%)	2 (0.8%)	17 (4.6%)	
Ocular	6 (1.0%)	2 (0.8%)	4 (1.1%)	
Other	2 (0.3%)	0 (0.0%)	2 (0.5%)	
AJCC Stage of disease at first metastasis, no. (%)				<.0001
III	274 (44.9%)	82 (33.7%)	190 (51.8%)	
IV	336 (55.1%)	161 (66.3%)	177 (48.2%)	
BRAF status				.4
<i>BRAF V600</i> mutant	120 (19.7%)	54 (22.2%)	66 (18.0%)	
<i>BRAF V600</i> wild-type	159 (26.1%)	61 (25.1%)	98 (26.7%)	
Unknown	331 (54.3%)	128 (52.7%)	203 (55.3%)	
Class of systemic therapies ^b				.5 .5 .7 1.0
BRAF pathway inhibitor	90 (14.8%)	39 (16.0%)	51 (13.9%)	
Interleukin-2	80 (13.1%)	35 (14.4%)	45 (12.3%)	
Anti-CTLA-4	188 (30.8%)	77 (31.7%)	111 (30.2%)	
Anti-PD-1/PD-L1 therapy	50 (8.2%)	20 (8.2%)	30 (8.2%)	

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; MBM, melanoma brain metastases; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

^a Age at the date of first regional or distant metastasis.

^b Only first-line through third-line therapies.

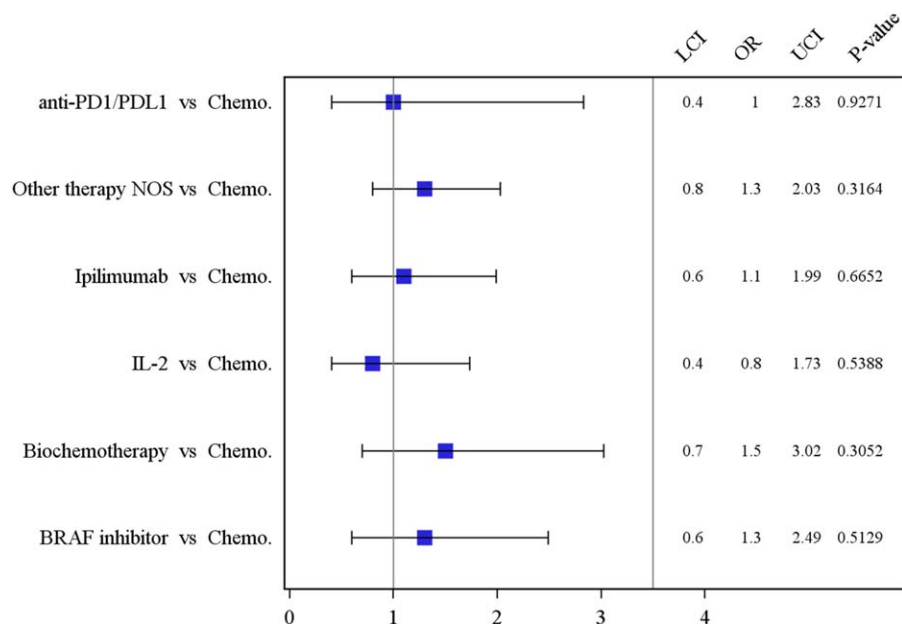


Figure 1. Forest plot of odds of the risk of developing de novo melanoma brain metastases (MBM) during systemic therapy. Odds ratio (OR) of developing de novo MBM with each class of therapy was determined using chemotherapy (chemo) as the denominator. 95% confidence intervals were reported. IL-2 indicates interleukin-2; LCI, lower confidence interval; NOS, not otherwise specified; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1; UCI, upper confidence interval.

primary MBM was SRS in 118 patients (48.6%), followed by whole-brain radiotherapy (WBRT) in 38 patients (15.6%), craniotomy in 37 patients (15.2%), start of new systemic treatment in 3 patients (1.2%), and continuation

of prior systemic treatment in 2 patients (1.0%). Of the 243 patients with MBM, 13 (5.4%) received no treatment. The remainder of patients received combination treatments such as SRS plus WBRT.

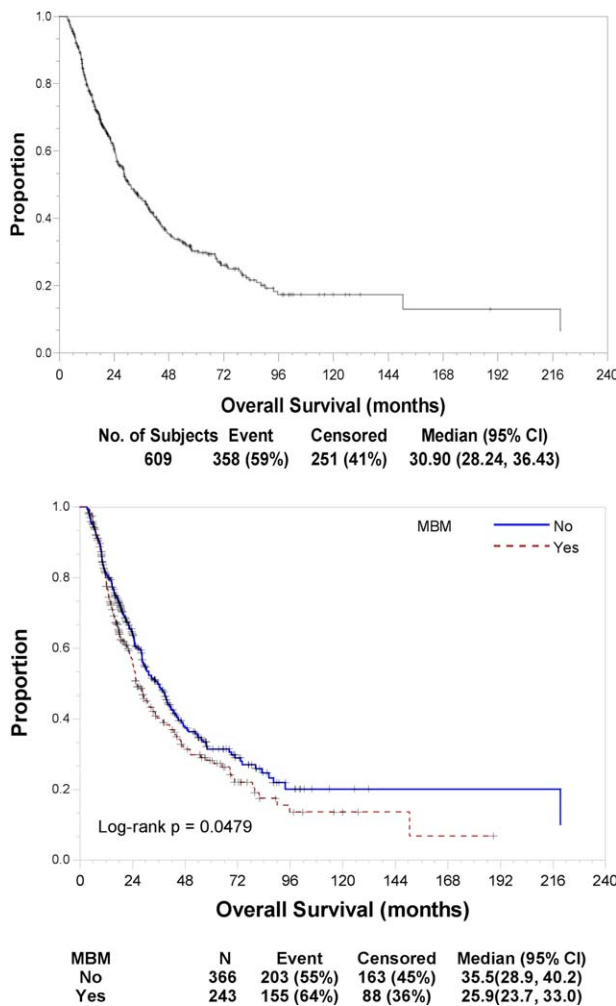


Figure 2. Overall survival (OS) from the date of first regional or distant metastasis to death. (A) OS for all patients. (B) OS for patients diagnosed with melanoma brain metastases (MBM) compared with those with no MBM diagnosis during the course of the disease. Tick marks represent patient censoring. 95% CI indicates 95% confidence interval.

Development of De Novo MBMs During the Administration of Systemic Therapy

The association between patient age, line of systemic therapy, and class of systemic therapy (first-line through third-line only) and the de novo MBM incidence rates were investigated using a GEE model to account for multiple lines of treatment received by the same patient. Patients with recurring MBM were censored for subsequent therapies. Although there was a trend toward an association between age and risk of developing de novo MBM ($P = .08$), no association was demonstrated between the line of therapy or class of systemic therapy and the risk of developing de novo MBM ($P = .68$ and $.85$, respectively). With regard to the latter using

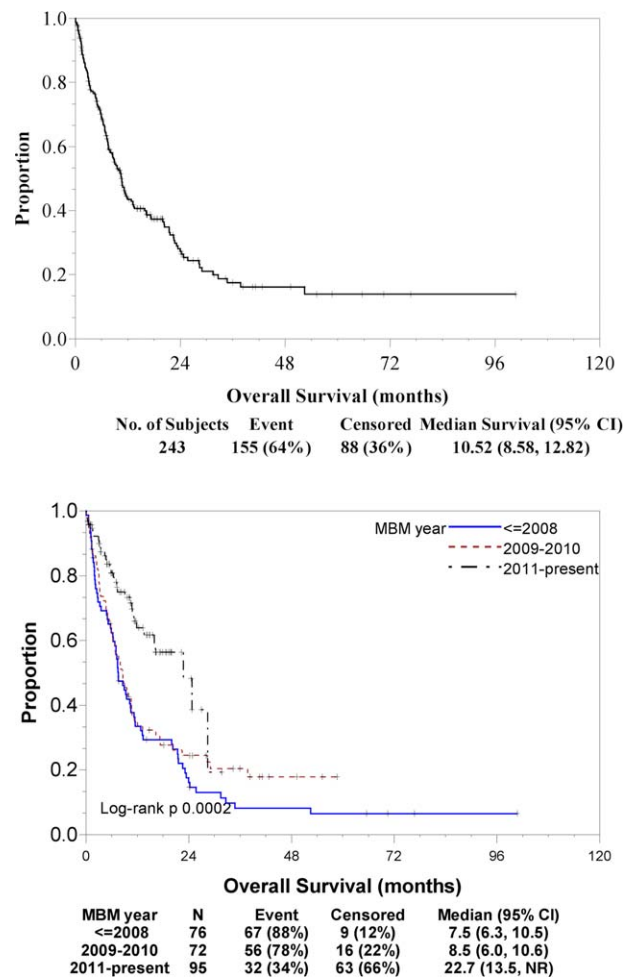


Figure 3. Overall survival (OS) of patients with melanoma brain metastases (MBM) from the date of first MBM diagnosis to death. (A) OS for all patients with MBM. Survival at 12, 24, and 36 months was 43.4% (95% confidence interval [95% CI], 36.6%-50.1%), 27.3% (95% CI, 20.5%-34.4%), and 17.5% (95% CI, 11.3%-24.9%), respectively. (B) OS for patients with MBM by year group of MBM diagnosis. NA indicates not available.

chemotherapy as the reference group, the odds ratios for developing de novo MBM were 1.5 (95% CI, 0.70-3.02) with biochemotherapy, 1.1 (95% CI, 0.60-1.99) with ipilimumab, 1.0 (95% CI, 0.40-2.83) with anti-PD-1/anti-PD-L1, and 1.3 (95% CI, 0.60-2.49) with BRAF-targeted therapy (Fig. 1).

Overall Survival

OS, defined as the duration from the date of first metastasis to death, was evaluated by Kaplan-Meier analysis for all patients (Fig. 2A). The median OS for all patients was 30.9 months (95% CI, 28.2-36.4 months). Survival probabilities at 1 year, 2 years, and 3 years were 79.7% (95% CI, 76.3%-82.8%), 60.6% (95% CI, 56.3%-64.6%),

TABLE 2. Multivariate Cox Model for MBM Prognostic Factors

Parameter	Comparison	HR (95% CI)	P
MBM y of diagnosis	≤2008 vs 2011-present	1.98 (1.10-3.56)	.0226
	2009-2010 vs 2011-present	2.77(1.58-4.87)	.0004
No. of MBM	2-4 vs 1	1.52 (0.92-2.52)	.1038
	≥5 or leptomeningeal vs 1	1.95 (1.04-3.66)	.0374
Neurologic symptoms	Yes vs no	1.95 (1.16-3.30)	.0123
MBM line of systemic therapy	1/1-2 vs 0 (before systemic therapy)	1.20 (0.71-2.04)	.4999
	2/2-3 vs 0 (before systemic therapy)	4.72 (2.55-8.72)	<.0001
	≥3 vs 0 (before systemic therapy)	1.64 (0.86-3.12)	.1310
MBM primary treatment	None vs SRS	2.66 (1.13-6.25)	.0254
	Surgery vs SRS	1.50 (0.77-2.94)	.2312
	WBRT vs SRS	0.98 (0.54-1.75)	.9309
KPS	≤70 vs >90-100	2.41 (1.19-4.86)	.0142
	>70-90 vs >90-100	1.08 (0.65-1.78)	.7708

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; MBM, melanoma brain metastases; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

and 45.9% (95% CI, 41.4%-50.3%), respectively. OS was significantly different between patients with and those without MBM (median OS: 25.9 months vs 35.5 months, respectively [$P = .048$]) (Fig. 2B). The 3-year OS rates were 40.2% (95% CI, 33.3%-47.0%) for patients with MBM and 49.8% (95% CI, 43.9%-55.5%) for patients without MBM. Because fewer patients with an MBM diagnosis had regional disease as their first metastasis, OS also was evaluated from the time of the initiation of first systemic therapy to death for further characterization (see Supporting Information Fig. 2). The median OS from the date of first systemic therapy was 20.3 months (95% CI, 16.9-24.9 months) for patients without MBM and 14.7 months (95% CI, 13.0-21.5 months) for patients with MBM ($P = .1755$).

Data then were analyzed separately in the MBM cohort. The median OS from the date of MBM diagnosis to the date of death was 10.5 months (95% CI, 8.6-12.8 months) (Fig. 3A). Survival probabilities at 1 year, 2 years, and 3 years were 43.4% (95% CI, 36.6%-50.1%), 27.3% (95% CI, 20.5%-34.4%), and 17.5% (95% CI, 11.3%-24.9%), respectively.

Prognostic Factors for Patients With MBM

Variables previously identified as being associated with MBM prognosis were evaluated by Kaplan-Meier analysis (using survival from the date of MBM diagnosis to death). These included age, sex, *BRAF V600* mutation status, number of MBM, neurologic symptoms, KPS, Diagnosis-Specific Graded Prognostic Assessment (DS-GPA), and primary type of MBM management (see Supporting Information Table 1). MBM year of diagnosis and line of therapy administered when MBM first developed were included in the analysis as well. Of these

factors, longer OS was associated with a later year of MBM diagnosis (2011-present), fewer MBM (1 or 2-4 MBM), the absence of neurologic symptoms, primary treatment of MBM (SRS or craniotomy), and better KPS/DS-GPA scores (all $P < .05$) (see Supporting Information Table 2). In particular, the median OS was 22.7 months in patients who were diagnosed with MBM in 2011 or later, compared with 8.5 months and 7.5 months, respectively, for patients diagnosed with MBM between 2009 and 2010 and 2000 and 2008 ($P = .0002$) (Fig. 3B).

Similar findings were observed using a univariate Cox model to study variables associated with the risk of death in patients with MBM (see Supporting Information Table 3). Statistically significant variables (MBM year of diagnosis, number of MBM, neurologic symptoms, KPS, and primary MBM treatment) then were analyzed using a multivariate Cox model (Table 2). DS-GPA was not included because it incorporates both the number of MBM and KPS. All variables demonstrated statistically significant independent associations with risk of death. The risk of death was 2.8-fold and 2.0-fold greater, respectively, for patients diagnosed with MBM between 2009 and 2010 and 2000 and 2008 when compared with those diagnosed between 2011 to the time of last follow-up. HRs for risk of death in patients with 2 to 4 MBM and ≥5 MBM and/or leptomeningeal disease were 1.5 and 2.0, respectively, compared with for patients with 1 MBM. Patients with neurologic symptoms had an HR of 2.0 compared with asymptomatic patients with MBM. Although a KPS of ≤70 had an HR of 2.4 compared with a KPS >90 to 100, there was no significant difference noted between a KPS of 70 to 90 and a KPS of >90 to 100. Receipt of BRAF-targeted therapy and/or immune checkpoint therapy was analyzed to determine the

association with MBM year of diagnosis for contribution toward improved OS. The majority of patients (72%) who received ≥ 1 of these therapies were diagnosed with their first MBM in 2011 or after (chi-square, 92.13; $P < .0001$). Furthermore, receipt of BRAF-targeted therapy and/or immune checkpoint therapy was found to be associated with improved OS using a multivariate Cox model (see Supporting Information Table 4). However, the significance was diminished when both MBM year of diagnosis and type of therapy received were included in the model (data not shown).

DISCUSSION

In the current retrospective study, MBM incidence and MBM patient survival were investigated and compared with outcomes of patients with advanced stage disease without MBM. To the best of our knowledge, this resulted in one of the largest MBM cohorts reported to date with the inclusion of patients receiving approved BRAF-targeted and immune checkpoint therapy. The following key observations were made: 1) the overall incidence of de novo MBM in patients with advanced melanoma who were receiving systemic therapy was 40%, which primarily occurred before or during the first line of therapy; 2) the incidence of MBM was not significantly different with BRAF-targeted agents, ipilimumab, or anti-PD-1/PD-L1 therapy compared with traditional chemotherapy; 3) the median OS of patients with MBM was statistically shorter than that of patients without MBM from the time of first regional or distant metastasis but not from the initiation of first-line systemic therapy; and 4) the median OS of patients with MBM was significantly longer in patients diagnosed with MBM in 2011 or after, which was independent of other MBM prognostic factors.

The MBM incidence rate in the current study is consistent with past studies in which 44% of patients with melanoma with unresectable stage III/IV disease developed MBM.^{1,27} In addition, the lack of an association between BRAF status and MBM incidence was similar to that of several prior retrospective studies.^{5,8,27} However, BRAF status was unknown in approximately 37% of the patients in current study due to BRAF testing not being routinely conducted before the approval of vemurafenib in 2011, which may have impacted the results. With regard to the timing of de novo MBM, patients were most likely to be diagnosed before or during the first line of systemic therapy (27% of all patients). This supports National Comprehensive Cancer Network recommendations for the inclusion of brain imaging for the initial staging and monitoring of patients with advanced

melanoma.²⁸ The fact that patients still were diagnosed frequently with de novo MBM during second-line therapy and after also supports the need for continued surveillance in patients undergoing therapy; however, to the best of our knowledge, the frequency with which to screen for MBM is not well defined.

Contrary to what may have been expected, the rate of de novo MBM was not found to be significantly lower in patients treated with newer targeted and immunotherapy agents that demonstrate objective CNS antitumor activity.¹⁸⁻²¹ For selective BRAF inhibitors, limited drug penetration across the blood-brain barrier and possible brain-derived factors produced from astrocytes that enhance tumor survival may be contributing factors.^{29,30} In a similar fashion, the CNS has been described as an immune privileged site in which direct stimulation or recruitment of cytotoxic T-cell populations may be less robust compared with extracranial tumor sites treated with immunotherapy.³¹ Another possibility is that neither class of therapies directly target the biology underlying brain tropism for some melanoma tumors.^{7,32}

Encouragingly, the median OS of patients with MBM in the current data set appears much improved compared with historical data. Davies et al reported a median OS of 4.7 months after a diagnosis of MBM in patients who developed MBM during clinical trial participation between 1986 and 2004.¹ In the current study, the median OS was 10.5 months from the time of MBM diagnosis for the entire MBM patient population, which was driven largely by substantially improved survival observed in patients diagnosed in 2011 or after (median, 22.7 months for this patient population). The results of the current study are supported by multiple smaller retrospective studies in which the median survival for patients with MBM treated with SRS and either BRAF therapies or immune checkpoint therapy has been 1 to 2 years.³³⁻⁴⁰ More important, the gap in OS between patients with and without MBM appears to be narrowing and was not found to be statistically significant in the current study when determined from the time of first systemic therapy.

The current study has several limitations. By identifying patients largely based on systemic therapy records, patients with MBM who never received systemic treatment due to cure by craniotomy or SRS or death occurring before therapy were not captured. The exclusion of patients with < 2 months of follow-up while receiving systemic therapy might have added to this latter bias, causing an overestimation of OS. However, this type of bias is present in other published studies (eg, Davies et al¹). Another limitation is the potential variability of surveillance brain

imaging. Many of the patients receiving BRAF-targeted and immune checkpoint therapies participated in clinical trials in which brain imaging routinely was performed and could have introduced a lead time bias. Inevitably, bias arises from separating treatments out by line of therapy. Current cancer care has become increasingly complex and many patients with MBM receive a combination of therapies, both brain-directed therapies such as WBRT/SRS and systemic therapies. Last, the focus of the current study was on the development of de novo MBM during systemic therapy. Tracking progression in treated patients with MBM and the development of subsequent MBM was beyond the scope of this investigation.

The development of brain metastases remains a clinical problem despite better OS in patients diagnosed since the introduction of BRAF-targeted and immune checkpoint therapies. This is in part reflective of the major advances in treating extracranial disease and more effective localized MBM control with craniotomy and SRS. The exclusion of patients with treated MBM from clinical trials is not appropriate given the more favorable survival of patients with MBM. Future research concerning strategies to abrogate the development of MBM is warranted.

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CONFLICT OF INTEREST DISCLOSURES

Sarah Sloot received financial support from a grant from the Melanoma Sarcoma Groningana Foundation for work performed as part of the current study and has acted as a medical advisor and field medical director for Pfizer for work performed outside of the current study after data for the current study were collected. Jeffrey S. Weber has acted as a consultant and member of the advisory boards of Bristol-Myer Squibb, GlaxoSmithKline, Genentech, Novartis, Merck, AstraZeneca, Nektar, Medivation, Roche, Celldex, Incyte, and EMD Serono; has participated in advisory boards for Lion Bioscience, Celldex, CytomX Therapeutics, and cCAM Biotherapeutics; received research support from Mirati Therapeutics and Acetylon Pharmaceuticals; holds equity in Celldex, CytomX Therapeutics, and Altor; and has a patent pending for an ipilimumab biomarker by Moffitt Cancer Center and a patent pending by Biodesix for a programmed cell death protein 1 (PD-1) biomarker. Jonathan S. Zager has participated in advisory boards for Amgen and Delcath systems; has served as a consultant for Castle Biosciences; and has received research support from Amgen, Delcath Systems, Provectus, and Castle Biosciences for work performed outside of the current study. Vernon K. Sondak has participated in advisory boards for Merck, Genentech/Roche, Provectus, Bristol-Myers Squibb, and Novartis, and has served on data safety monitoring boards for Bristol-Myers Squibb, Array Biopharma, Novartis, Polynoma, and Pfizer for work performed outside of the current study. Geoffrey T.

Gibney has served as a consultant for Novartis and Genentech/Roche, and as a member of the Speakers' Bureau for Merck and Genentech for work performed outside of the current study.

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